

Synthesis of Aminopyran Using Green Catalyst at Room Temperature

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOPACS/2017/38728

Editor(s):

(1) Mustafa Boyukata, Professor, Department of Physics, Bozok University, Turkey.

Reviewers:

(1) Zuoxiang Zeng, East China University of Science and Technology, China.

(2) Subhash Banerjee, Guru Ghasidas Vishwavidyalaya, India.

Complete Peer review History: <http://www.sciencedomain.org/review-history/22859>

Original Research Article

Received 24th October 2017

Accepted 16th January 2018

Published 25th January 2018

ABSTRACT

A simple, efficient and step-economy one-pot synthesis to afford the library of Ethyl 6-amino-4-phenyl-5-cyano-2-methyl-4H-pyran-3-carboxylate derivatives from readily available substrates malononitrile, an active methylene group and substituted aromatic aldehyde using novel heterogeneous calcined Mg-Fe-CO₃ hydrotalcite at room temperature. The calcined Mg-Fe hydrotalcite with the molar ratio of 3:1 derived from calcination at 500°C was found to be a suitable catalyst that gives the highest basicity and best catalytic activity. The catalysts were characterized by XRD, TGA, SEM and Hammett titration method. The reaction is rapid, clean, easy to work up, high activity of the catalyst and gives a product in high yields. The catalyst is reusable. However, the yield of product remains same even after reusing of catalyst number of times.

Keywords: Hydrotalcite; heterogeneous catalyst; aminopyran; multicomponent; aromatic aldehyde.

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1. INTRODUCTION

One-multicomponent reactions are processed in which complicated molecules, especially synthesis of the heterocyclic compound with biological and medicinal properties in a very fast, efficient and economic manner without isolation of an intermediate [1]. Hence, multicomponent reactions have great ability to build one product in a single operation [2] by virtue of their convergence, facile execution, productivity and generation of complex and highly diverse products from easily available three or more reactant molecules with high atom economy [3] and multiple bonds forming efficiency [4]. There has been a great development in three or four component reactions and effort are still being made to develop a new multicomponent reaction [5].

As an important class of oxygen-containing heterocycles, aminopyran are widely used as antitumor [6], antiallergic [7] and antibacterial [8]. In addition, they can be used as a selective inhibitor of excitatory amino acid transporter sub-type 1 [9] and IKC channel blockers [10].

Pyran derivatives have versatile application in the field of organic synthesis and its application in medicinal chemistry, many researchers have been involved to develop a highly efficient procedure for this kind of compound. The straightforward synthesis of heterocyclic moiety involves two-step reaction carried out between Michael acceptor (arylidene malononitrile) and β -dicarbonyl compound in the presence of organic bases such as triethylamine [11], piperidine [12] and pyridine [13].

A variety of methods have been used to synthesize aminopyran which involve several catalysts such as InBr_3 [14], $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}\cdot 18\text{H}_2\text{O}$ [15], $\text{KF/Al}_2\text{O}_3$ [16], Mg/La mixed oxide [16]. In addition to above, other non-catalytic protocols such as electro-oxidation [17] and combined ultrasound and microwave irradiation [18] are employed. Each of the above methods has its own merits but all of these include some or other drawbacks such as the use of a catalyst that is expensive and harmful to the environment, high temperature, tedious workup, long reaction time, poor product yields, difficulties in recovery of catalysts. Consequently, gaps remain in terms of a search of alternative methodologies for aminopyran synthesis which is highly efficient and clean.

As our interest in heterogeneous catalyst application in organic synthesis, herein we present the exploitation of economically attractive and easily available Mg/Fe hydrotalcite as an environmentally friendly catalyst. In view of easy recovery and subsequent reuse, heterogeneous catalyst always superior to their homogeneous counterparts. Hydrotalcite and modified Hydrotalcites have an application such as for isomerization reaction [19], Michael addition [20] and epoxidation of α, β -Unsaturated Ketenes' [21].

We have developed green methodologies for the synthesis of heterocycles with Mg/Fe hydrotalcite, a heterogeneous base catalyst that catalyzed three component condensation of an aromatic aldehyde, malononitrile and ethyl acetoacetate at room temperature.

2. MATERIALS AND METHODS/ EXPERIMENTAL DETAILS

2.1 Materials and Methods

2.1.1 Materials

All chemicals such as Substituted benzaldehyde, Magnesium nitrate, Ferric nitrate, Sodium carbonate, Sodium hydroxide, Ethyl acetoacetate and diketones etc. of A.R. grade were purchased from S.D. Fine Chemicals Ltd., Mumbai, India and were used without any further purification.

2.1.2 Method of characterization

Melting points of all synthesized compounds were measured on electrothermal apparatus using open capillary tubes and are uncorrected. Thin Layer Chromatography for a purity of compounds was performed on silica gel coated aluminium plate as adsorbent and which are analyzed with U.V. light as the visualizing agent. FT-IR Spectra were recorded on Bruker Spectrometer in the region of $400\text{-}4000\text{ cm}^{-1}$. ^1H and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using TMS as an internal standard and $\text{CDCl}_3/\text{DMSO-d}_6$ as solvent (chemical shifts in δ ppm).

Powder X-ray diffraction pattern was collected with monochromatic $\text{Cu K}\alpha$ radiation ($\lambda = 1.54059\text{ \AA}$) at 40 kV and 15 mA using Shimadzu 7000S diffractometer. Thermogravimetric analysis was performed with a RIGAKU Thermo Plus TG 8120 thermobalance with a heating rate of $(10^\circ\text{C}/\text{min})$ from 25 to 900°C . The

morphological information gathered using scanning electron microscope ZEISS Ultra FESEM.

2.2 Experimental Details

2.2.1 Catalyst preparation

Mg-Fe Hydrotalcites with different Mg/Fe molar ratio (Mg/Fe = 2:1, 3:1, 4:1 and 5:1) were synthesized by co-precipitation method [22]. An aqueous solution of Mg (NO₃)₂·6H₂O and Fe (NO₃)₂·9H₂O were prepared and mixed aqueous solution of Mg(NO₃)₂·6H₂O and Fe(NO₃)₂·9H₂O was added dropwise using addition funnel to an aqueous solution containing NaOH and Na₂CO₃ under vigorous stirring. After complete addition, the solution was heated at 80°C for 18 hr and maintain pH of the solution in the range of 10-11 during stirring. After complete stirring, the solution was allowed to cool at room temp and filtered. The obtained residue was washed with hot deionized water several times till filtrate was neutral. The solid was dried in an oven at 60°C in air. Dry solid then calcined at 500°C for 5 hrs.

2.2.2 General procedure for synthesis of Aminopyran

In 50 ml round bottom flask, aryl aldehyde (3 mmol), malonitrile (3 mmol), ethyl acetoacetate (3 mmol) and C-Mg-Fe hydrotalcite (0.3 gm) in ethanol (5 ml) were stirred at room temperature till the reactant was fully consumed. The reaction was monitored by Thin Layer Chromatography using ethyl acetate and pet ether (2:8). After completion of the reaction, the reaction mixture was heated to dissolve the product in ethanol and the solution filtered hot. The filtrate was evaporated and the solid product

was obtained. This product was recrystallized using hot ethanol to afford pure product. Purified product characterized by ¹H N.M.R. and ¹³C NMR.

3. RESULTS AND DISCUSSION

XRD Spectral data of calcined Mg/Fe = 3 hydrotalcite catalyst is matched with according to standard hydrotalcite peaks, as indexing value are correlating with the reported hydrotalcites. After calcination of catalyst, mixed oxides of hydroalcite are formed due to loss carbonate and water from the hydrotalcite. The powder X-ray diffraction pattern of Layer Double Hydroxide with Mg/Fe=3:1 molar ratio (Fig. 1) shows peaks at 2θ = 43.14°, 62.60° which are corresponding to MgO and at 2θ = 30.14°, 35.52°, 43.14° and 62.60° which can be attributed to MgFe₂O₄ spinel structure (JCPDS 17-0465) that peak have been reported in literature [23].

As per TGA plot of Mg/Fe molar ratio 3:1 shows three distinct phase loss in the temperature range of 50-200°C, 200-460°C and 460- 750°C (Fig. 2). The first weight loss in the temp range of 50-200°C mainly due to interlayer and physisorbed water. This weight loss was about 13%. Further weight loss observed is 21% which occurs between 200-460°C as a result of carbonate ions removal from the interlayer of hydrotalcite and first step dehydroxylation. In continuation of heating to 460°C leads to dehydroxylation and decarbonation and formation of oxide metals as MgO which are detected in X-ray diffraction of calcined Layer Double Hydroxide and possibly MgFe₂O₄. as reported in the literature [24]. There was no significant mass loss of catalyst observed beyond 600°C temperature.

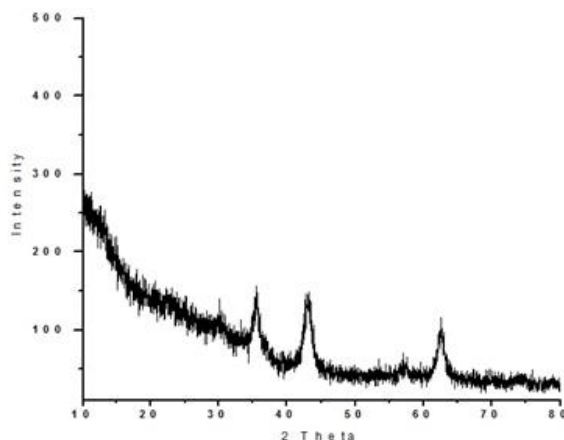


Fig. 1. XRD spectrum for hydrotalcite with Mg/Fe=3:1 calcined at 500°C

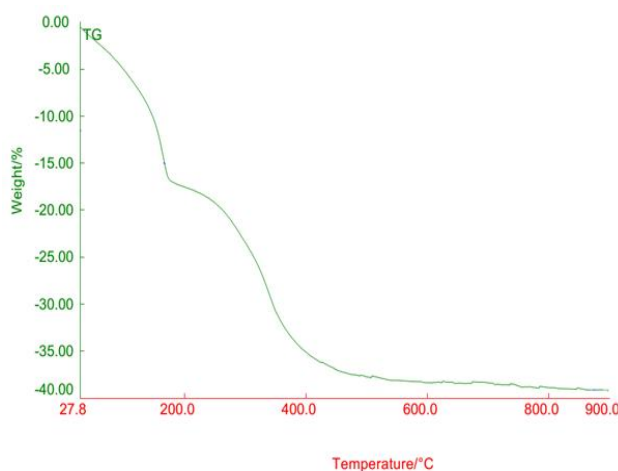


Fig. 2. TGA plot of hydrotalcite with Mg/Fe=3:1

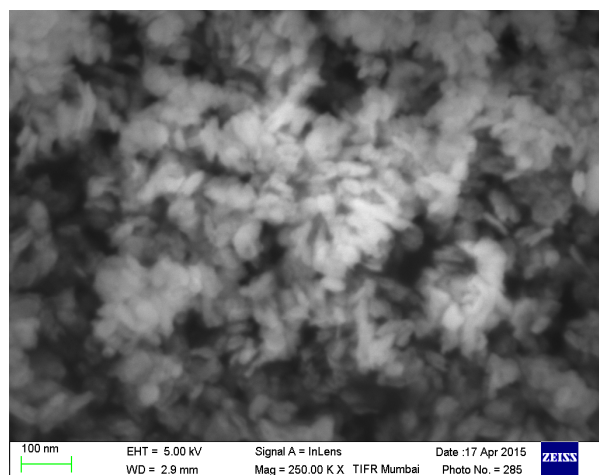


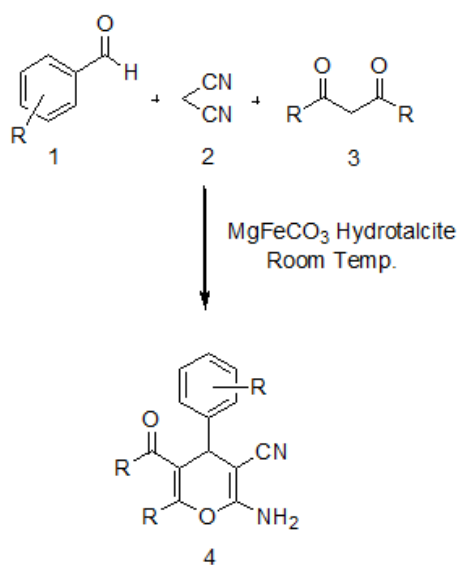
Fig. 3. SEM image of calcined hydrotalcite with Mg/Fe=3:1

The SEM image of C-Mg-Fe-HT-3 showed the Homogeneity in shapes and high crystallinity for the calcined catalyst (Fig. 3).

The reaction of benzaldehyde, malonitrile and ethyl acetoacetate was selected as a model reaction (Scheme 1) for optimization of various parameters such as the quantity of catalyst, reaction medium and nature of the catalyst at room temperature using Mg/Fe hydrotalcite as a heterogeneous basic catalyst.

The mechanism of this reaction is interesting because pK_a values of malonitrile and ethyl acetoacetate are nearly the same i.e 11.2 and 11.0 respectively. When the reaction of benzaldehyde with malonitrile was carried out at room temperature, it took place within 10 minutes in the presence of C-Mg/Fe HT-3, while

the reaction of benzaldehyde with ethyl acetoacetate did not happen under the same condition. Hence, the reaction of benzaldehyde with malonitrile in presence of C-Mg/Fe HT-3 leads to the formation of benzylidene malonitrile. The intermediate has a high polarized bond to which ethyl acetoacetate add under the same condition and the resulting adduct cyclizes to the product. The crucial factor for multicomponent reaction is proper selection of solvent. So, at the initial stage, we looked into the solvent selection for this reaction. The reaction was run in different organic polar protic and aprotic solvents (Table 1) such as water, ethanol, methanol, DMF, DMSO. From results, we choose ethanol as an ideal solvent for this reaction. In this reaction solvent play an important role as the reaction under solvent-free condition gave a low yield of the product.



Scheme 1. Synthesis of Aminopyrans

Table 1. Influence of different solvent in reaction of benzaldehyde with malononitrile and ethyl acetoacetate at ambient temperature

Entry	Solvent	Yield of product (%)
1	H ₂ O	52
2	EtOH	96
3	MeOH	85
4	DMF	65
5	DMSO	62
6	WITHOUT SOLVENT	50

Reaction condition: Benzaldehyde (3 mmol), malononitrile (3 mmol), ethyl acetoacetate (3 mmol), solvent (5 ml), C-Mg-Fe HT-3 (0.3 g), ambient temperature (29°C).

Apart from the solvent, the effectiveness of MCR is depended on the catalyst (Table 2) and catalyst quantity (Table 3). The reaction was carried out using calcined catalyst (Mg/Fe= 2:1, 3:1, 4:1, 5:1). After screening of The calcined hydrotalcites, hydrotalcite having Mg/Fe molar ratio 3:1 gave a good yield of the product. In absence of catalyst, the reaction did not progress. Mg/Fe hydrotalcite having a different molar ratio (Mg/Fe=2:1, 3:1, 4:1, 5:1.) and temperature showed a greater effect on basicity. The Lewis basicity of catalyst increases, while Bronsted basicity decreases at high temperature. It is reported that calcined hydrotalcite contains surface basicity due to OH⁻ group, (Mg-O) pairs

and (O²⁻) species [25]. The basicity of Hydrotalcite's sensitive to the Mg/Fe ratio. The total basicity of catalyst increases gradually with Mg/Fe molar ratio and comes to a maximum at the Mg/Fe ratio of 3:1. Further increase in molar ratio of Mg/Fe hydrotalcite decreases the basicity.

Table 2. Influence of Mg-Fe-Hydrotalcite catalyst with the different molar ratio in reaction of benzaldehyde with malononitrile and ethyl acetoacetate at ambient temperature

Entry	Hydrotalcite	Yield of product (%)
1	C-MG-FE HT-2	45
2	C-MG-FE HT-3	96
3	C-MG-FE HT-4	65
4	C-MG- FE HT-5	55
5	WITHOUT HT	NO REACTION

Reaction condition: Benzaldehyde (3 mmol), malononitrile (3 mmol), ethyl acetoacetate (3 mmol), EtOH (5 ml), catalyst (0.3 g), ambient temperature (29°C).

To find out the optimize catalyst quantity, the reaction was carried out using different catalyst quantities. The calcined Mg-Fe HT-3 (0.3 gm) found to be optimal quantity (Table 3). Further increase in the catalyst quantity beyond 0.3 gm did not showed significant increase in the yield.

Table 3. Influence of C-Mg-Fe-Hydrotalcite-3 catalyst loading in reaction of benzaldehyde with malononitrile and ethyl acetoacetate at ambient temperature

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.1	45
2	0.2	62
3	0.3	96
4	0.4	96
5	0.5	96

Reaction conditions: Benzaldehyde (3 mmol), malononitrile (3 mmol), ethyl acetoacetate (3 mmol), EtOH (5 ml), ambient temperature (29°C).

Hydrotalcite as a heterogeneous catalyst, so it could be easily separated from the reaction mixture by simple filtration and recovered catalyst was used for successive runs to check it's reusability (Fig. 4).

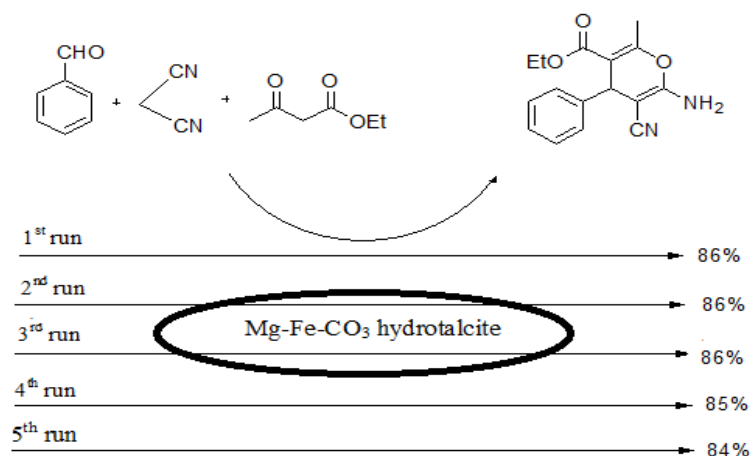


Fig. 4. Reusability of C-Mg-Fe- HT- 3 catalyst.

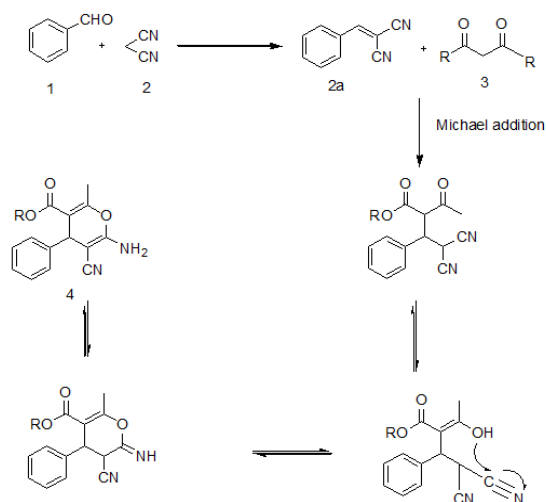
Reaction conditions: Benzaldehyde (3 mmol), malononitrile (3 mmol), ethyl acetoacetate (3 mmol), EtOH (5 ml), C-Mg-Fe- HT- 3 (0.3 g), ambient temperature (29°C).

It was observed that there was no significant decrease in the yield of the product (%). Under the above-optimized reaction parameter, different substituted aromatic aldehyde was reacted with malononitrile and ethyl acetoacetate to obtain corresponding aminopyrans in high yield are tabulated in (Table 4). The expected and better yield of product obtained in the aromatic aldehyde containing electron withdrawing group as compared to aromatic aldehydes with electron donating group. With the aim of generating sufficient diversity, the reaction of benzaldehyde and malononitrile with β -ketoester, β -diketone were attempted (Table 4). It was

found that cyclic β -diketone gave the better yield as compared acyclic β -diketone showed excellent reactivity with a high yield of the products (4a – 4g).

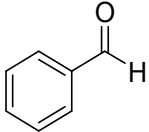
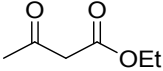
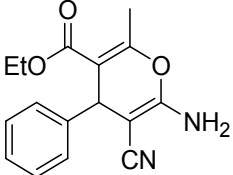
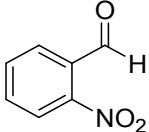
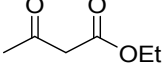
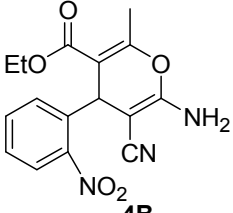
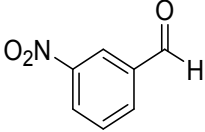
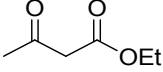
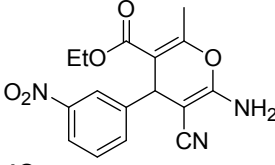
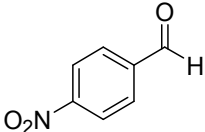
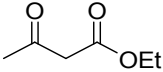
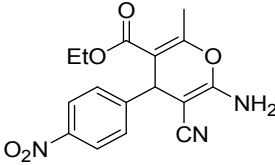
3.1 Mechanism

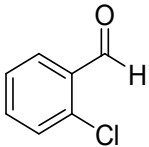
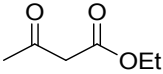
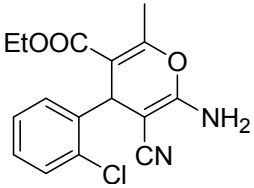
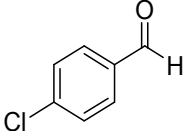
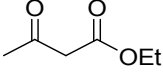
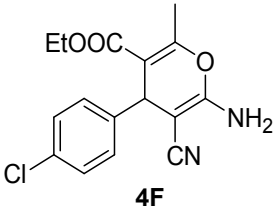
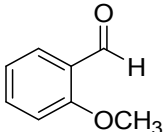
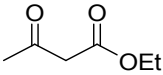
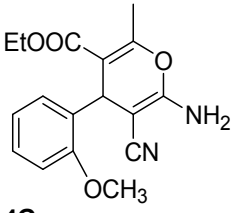
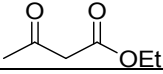
We propose a possible mechanism for the formation of product (4) (Scheme 2). It is suggested that the reaction proceeds in two steps: condensation of benzaldehyde (1) and malononitrile (2) according to Knoevenagel type reaction leads to the formation of benzylidene malononitrile (2a). The intermediate (2a) has a highly polarized double bond, to which ethyl acetoacetate (3) adds under the same conditions and the resulting adduct cyclizes to the derivative of aminopyran product (4).

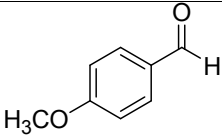
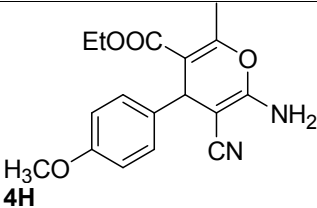
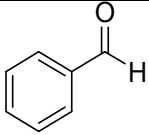
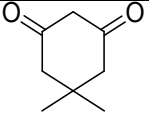
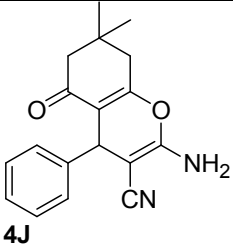
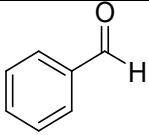
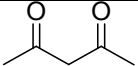
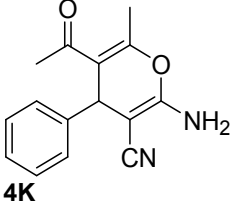


Scheme 2. Proposed reaction mechanism

Table 4. One pot synthesis of 2-amino-4H-pyrans derivatives

Er. no.	Substituted benzaldehyde	Active methylene group	Product	Yield (%)	Time (min)	Observed M.P.(°C)	Reported M.P.(°C)
1			 4A	86	60	176-178	178-180[26]
2			 4B	84	50	178-180	177-178[27]
3			 4C	88	45	183-184	182-183[28]
4			 4D	87	35	179-180	180-183[28]

Er. no.	Substituted benzaldehyde	Active methylene group	Product	Yield (%)	Time (min)	Observed M.P.(°C)	Reported M.P.(°C)
5			 4E	84	50	190-192	191-192[29]
6			 4F	85	50	174-175	175-177[30]
7			 4G	78	80	194-196	196-197[27]
8				80	70	157-159	158-164[32]

Er. no.	Substituted benzaldehyde	Active methylene group	Product	Yield (%)	Time (min)	Observed M.P.(°C)	Reported M.P.(°C)
							
9				89	30	223-224	224-225[31]
10				80	70	157-159	158-164[32]

Spectral data:

Ethyl 6-amino-4-(phenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (Entry No.-1)

Colorless solid, M.P. =176-178°C,

¹H-NMR (500 MHz, DMSO-d₆, ppm):

δppm = 1.009(t,3H,CH₃), 2.482(s,3H,CH₃), 3.945(q,2H,CH₂), 4.272(s,1H,CH), 6.856(s,2H,NH₂), 7.118-7.303(m,5H,Ar-H).

¹³CNMR (500 MHz, DMSO-d₆, δppm):

δ=13.695(CH₃), 18.120(CH₃), 38.827(CH₂), 57.225(CH), 119.723(CN), 121.914-145.510(2x C=C,ArC), 165.434 (C=O).

Ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate

(EntryNo.-2) Colorless solid, M.P.=183-184°C,

¹H-NMR (500 MHz, DMSO-d₆, δppm):

δ ppm = 1.002 (t, 3H, CH₃), 2.481 (s, 3H, CH₃), 3.945 (q, 2H, CH₂), 4.504 (s, 1H, CH), 7.061 (s, 2H, NH₂), 8.009-7.612(m,4H,Ar-H),

¹³CMR (500 MHz, DMSO-d₆, δppm):

δ=13.767(CH₃), 18.225(CH₃), 38.646(CH₂), 57.318(CH), 119.535(CN), 121.914-147.647(2x C=C,ArC),165.065 (C=O).

4. CONCLUSION

Calcined Mg/Fe = 3 hydrotalcite act as an efficient catalyst for synthesis of aminopyran at room temperature. The present procedure is fast and gives an excellent yield of the product. The hydrotalcite solid catalyst may be reacted without appreciable loss of catalytic activity. The catalytic activities of the calcined hydrotalcite show a striking correlation with their corresponding basic properties. More ever it has several advantages easy separation of the catalyst by simple filtration, an inexpensive, environmentally friendly, high catalytic activity, and non-toxic.

ACKNOWLEDGEMENTS

The Authors are thankful to the principal and Management of Kishichand Chellaram College, Mumbai University, Churchgate, Mumbai-400

020. Authors are also thankful to TIFR, Mumbai for providing spectral data.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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